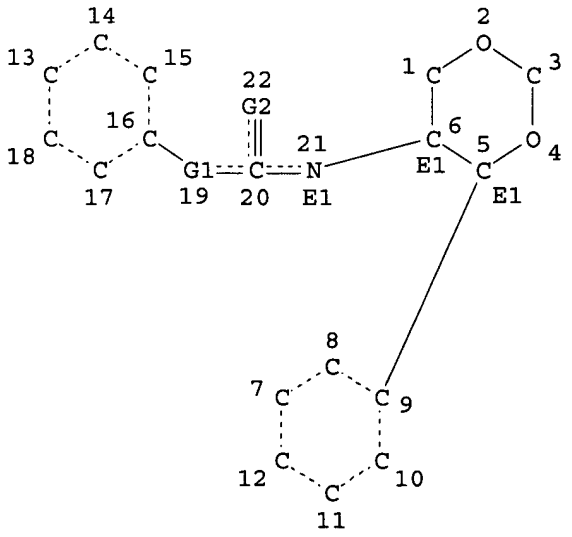
```
=> d his

     (FILE 'HOME' ENTERED AT 14:31:58 ON 21 DEC 2004)

     FILE 'REGISTRY' ENTERED AT 14:32:26 ON 21 DEC 2004
L1               STR
L2             3 S L1
L3            59 S L1 FUL

     FILE 'CHEMCATS' ENTERED AT 14:53:18 ON 21 DEC 2004
L4             9 S L3

     FILE 'BEILSTEIN' ENTERED AT 14:55:24 ON 21 DEC 2004

=> s l1
SAMPLE SEARCH INITIATED 14:55:34 FILE 'BEILSTEIN'
SAMPLE SCREEN SEARCH COMPLETED -       0 TO ITERATE

100.0% PROCESSED       0 ITERATIONS                                  0 ANSWERS
SEARCH TIME: 00.00.03

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:             0 TO         0
PROJECTED ANSWERS:                0 TO         0

L5             0 SEA SSS SAM L1

=> s l1 ful
FULL SEARCH INITIATED 14:55:47 FILE 'BEILSTEIN'
FULL SCREEN SEARCH COMPLETED -      15 TO ITERATE

100.0% PROCESSED      15 ITERATIONS                                  0 ANSWERS
SEARCH TIME: 00.00.09

L6             0 SEA SSS FUL L1

=> d sia
L6 HAS NO ANSWERS
L1               STR
```




```
VAR G1=NH/O/CH2
VAR G2=S/O/N
```

```
NODE ATTRIBUTES:
HCOUNT  IS E1     AT   5
HCOUNT  IS E1     AT   6
HCOUNT  IS E1     AT  21
CONNECT IS E2  R  AT   1
CONNECT IS E2  R  AT   3
CONNECT IS E2  R  AT   7
CONNECT IS E2  R  AT   8
CONNECT IS E2  R  AT  10
CONNECT IS E2  R  AT  11
CONNECT IS E2  R  AT  12
CONNECT IS E2  R  AT  13
CONNECT IS E2  R  AT  14
CONNECT IS E2  R  AT  15
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  22

STEREO ATTRIBUTES: NONE
L6             0 SEA FILE=BEILSTEIN SSS FUL L1


=>
```

```
*** YOU HAVE NEW MAIL ***

=> s oxerin-2 receptor
             0 OXERIN
       8247935 2
        582546 RECEPTOR
L1           0 OXERIN-2 RECEPTOR
                 (OXERIN(W)2(W)RECEPTOR)

=> s orexin-2 receptor
           867 OREXIN
       8247935 2
        582546 RECEPTOR
L2          37 OREXIN-2 RECEPTOR
                 (OREXIN(W)2(W)RECEPTOR)

=> s oxerin-1 receptor
             0 OXERIN
       8123919 1
        582546 RECEPTOR
L3           0 OXERIN-1 RECEPTOR
                 (OXERIN(W)1(W)RECEPTOR)

=> s orexin-1 receptor
           867 OREXIN
       8123919 1
        582546 RECEPTOR
L4          63 OREXIN-1 RECEPTOR
                 (OREXIN(W)1(W)RECEPTOR)

=> s mediated disease?
        405827 MEDIATED
        828105 DISEASE?
L5        2221 MEDIATED DISEASE?
                 (MEDIATED(W)DISEASE?)

=> s l5 (l) l2
L6           0 L5 (L) L2

=> s sleep wake disorder
         17495 SLEEP
          7008 WAKE
        243845 DISORDER
L7          12 SLEEP WAKE DISORDER
                 (SLEEP(W)WAKE(W)DISORDER)

=> s l7 and l2
L8           1 L7 AND L2

=> d cbib abs

L8   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2004 ACS on STN
2004:515499   Document No. 141:54349  Preparation of Substituted
     4-phenyl-[1,3]-dioxane as orexin-2 receptor
     ligands.  Carruthers, Nicholas I.; Jones, Todd K.; Li, Xiaobing;
     Lovenberg, Timothy W.; Mcatee, Laura C.; Phuong, Victor K.; Rudolph, Dale
     A.; Sutton, Steven W. (Janssen Pharmaceutica, N.V., Belg.).  PCT Int.
     Appl. WO 2004052876 A1 20040624, 83 pp.  DESIGNATED STATES: W:  AE, AG,
     AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ,
     DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
     IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG,
     MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE,
     SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA,
```

ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US40136 20031212. PRIORITY: US 2002-PV433192 20021212.

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [R2-6 = H, F, Cl, Br, I, etc.; X = NH, O, CH2; W = S, O, NCN; R7-8 = H, (cyclo)alkyl, etc.] are prepared For instance, (4S,5S)-2,2-dimethyl-4-phenyl-[1,3]dioxan-5-amine is reacted with 4-bromo-2-chlorophenylisocyanate to give II. II has Ki = 9 nM for the **orexin-2 receptor**. I are useful for the treatment of obesity or a **sleep/wake disorder** mediated by orexin-2.

=> d his

(FILE 'HOME' ENTERED AT 10:01:21 ON 22 DEC 2004)

FILE 'CAPLUS' ENTERED AT 10:01:55 ON 22 DEC 2004

L1	0	S	OXERIN-2 RECEPTOR
L2	37	S	OREXIN-2 RECEPTOR
L3	0	S	OXERIN-1 RECEPTOR
L4	63	S	OREXIN-1 RECEPTOR
L5	2221	S	MEDIATED DISEASE?
L6	0	S	L5 (L) L2
L7	12	S	SLEEP WAKE DISORDER
L8	1	S	L7 AND L2

=> d l2 ti tot

L2 ANSWER 1 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Novel substituted 4-phenyl-[1,3]dioxanes: potent and selective orexin receptor 2 (OX2R) antagonists

L2 ANSWER 2 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Method for identifying modulators of human **orexin-2 receptor**

L2 ANSWER 3 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Preparation of Substituted 4-phenyl-[1,3]-dioxane as **orexin-2 receptor** ligands

L2 ANSWER 4 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Merkel cells, a new localization of prepro-orexin and orexin receptors

L2 ANSWER 5 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Preparation of tetrahydroquinolines and tetrahydroisoquinolines as orexin receptor antagonists

L2 ANSWER 6 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Preparation of N-(arylsulfonyl) cyclic amines as orexin antagonists

L2 ANSWER 7 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Preparation of N-(arylacetyl) cyclic amine derivatives as orexin antagonists

L2 ANSWER 8 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Preparation of N-aroyl cyclic amines as orexin receptor antagonists

L2 ANSWER 9 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Characterisation of the binding of [3H]-SB-674042, a novel nonpeptide antagonist, to the human orexin-1 receptor

L2 ANSWER 10 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Structure-Activity Studies of Orexin A and Orexin B at the Human Orexin 1 and Orexin 2 Receptors Led to **Orexin 2** **Receptor** Selective and Orexin 1 Receptor Preferring Ligands

L2 ANSWER 11 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Preparation of 7,8,9,10-tetrahydro-6H-azepino, 6,7,8,9-tetrahydro-pyrido and 2,3-dihydro-2H-pyrrolo[2,1-b]-quinazolinone derivatives as orexin receptor antagonists

L2 ANSWER 12 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI N-Acyl 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline: The first **orexin-2 receptor** selective non-peptidic antagonist

L2 ANSWER 13 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI The orexin system in insulin resistance rat model induced by high-fructose diet

L2 ANSWER 14 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Preparation of piperazine derivatives as orexin receptor antagonists

L2 ANSWER 15 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Preparation of ethylene diamine derivatives as orexin receptor antagonists

L2 ANSWER 16 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI N-aroyl cyclic amine derivatives and their use as orexin receptor antagonist

L2 ANSWER 17 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Preparation of N-aroyl cyclic amine derivatives as orexin receptor antagonists

L2 ANSWER 18 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Preparation of piperazine bis-amide derivatives as antagonists of the orexin receptor

L2 ANSWER 19 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Preparation of N-aroyl piperazine derivatives as orexin receptor antagonists

L2 ANSWER 20 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Preparation of N-acyl-2-heterocyclyl substituted piperidines and analogs as orexin receptor antagonists

L2 ANSWER 21 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Orexins/hypocretins: neurotransmitters regulating sleep and appetite

L2 ANSWER 22 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Development of an **orexin-2 receptor** selective agonist, [Ala11, D-Leu15]orexin-B

L2 ANSWER 23 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Preparation of N-aroyl cyclic amines as orexin antagonists

L2 ANSWER 24 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Developmental changes in the **orexin 2 receptor** mRNA in hypoglossal motoneurons

L2 ANSWER 25 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Microinjection of orexin into the rat nucleus tractus solitarius causes increases in blood pressure

L2 ANSWER 26 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Preparation of morpholine derivatives as antagonists of orexin receptors

L2 ANSWER 27 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Effects of restricted feeding on the activity of hypothalamic Orexin (OX)-A containing neurons and OX2 receptor mRNA level in the paraventricular nucleus of rats

L2 ANSWER 28 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Protein distribution of the **orexin-2 receptor** in the rat central nervous system

L2 ANSWER 29 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Orexins Activate Histaminergic Neurons via the **Orexin 2 Receptor**

L2 ANSWER 30 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Preparation of piperidines as orexin receptor antagonists

L2 ANSWER 31 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Orexin/hypocretin excites the histaminergic neurons of the tuberomammillary nucleus

L2 ANSWER 32 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Protein and cDNA sequences of monkey **orexin 2 receptor** and uses in drug screening

L2 ANSWER 33 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Requirement of Intact Disulfide Bonds in Orexin-A-Induced Stimulation of Gastric Acid Secretion That Is Mediated by OX1 Receptor Activation

L2 ANSWER 34 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI A selective orexin-1 receptor antagonist reduces food consumption in male and female rats

L2 ANSWER 35 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Structure-activity relationship studies on the novel neuropeptide orexin

L2 ANSWER 36 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Distribution of orexin receptor mRNA in the rat brain. [Erratum to document cited in CA130:76402]

L2 ANSWER 37 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
TI Distribution of orexin receptor mRNA in the rat brain

=> d 3 10 12
1 ANSWERS ARE AVAILABLE. SPECIFIED ANSWER NUMBER EXCEEDS ANSWER SET SIZE
The answer numbers requested are not in the answer set.
ENTER ANSWER NUMBER OR RANGE (1):end

=> d l2 3 10 12

L2 ANSWER 3 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2004:515499 CAPLUS
DN 141:54349
TI Preparation of Substituted 4-phenyl-[1,3]-dioxane as **orexin-2 receptor** ligands
IN Carruthers, Nicholas I.; Jones, Todd K.; Li, Xiaobing; Lovenberg, Timothy W.; Mcatee, Laura C.; Phuong, Victor K.; Rudolph, Dale A.; Sutton, Steven

W.
PA Janssen Pharmaceutica, N.V., Belg.
SO PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004052876	A1	20040624	WO 2003-US40136	20031212
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004147593	A1	20040729	US 2003-734800	20031212
PRAI US 2002-433192P	P	20021212		

OS MARPAT 141:54349

L2 ANSWER 10 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2004:61288 CAPLUS
DN 140:263761
TI Structure-Activity Studies of Orexin A and Orexin B at the Human Orexin 1 and Orexin 2 Receptors Led to **Orexin 2 Receptor** Selective and Orexin 1 Receptor Preferring Ligands
AU Lang, Manja; Soell, Richard M.; Duerrenberger, Franz; Dautzenberg, Frank M.; Beck-Sickinger, Annette G.
CS Institute of Biochemistry, University of Leipzig, Germany
SO Journal of Medicinal Chemistry (2004), 47(5), 1153-1160
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 12 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:928900 CAPLUS
DN 140:174444
TI N-Acyl 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline: The first **orexin-2 receptor** selective non-peptidic antagonist
AU Hirose, Masaaki; Egashira, Shin-Ichiro; Goto, Yasuhiro; Hashihayata, Takashi; Ohtake, Norikazu; Iwaasa, Hisashi; Hata, Mikiko; Fukami, Takehiro; Kanatani, Akio; Yamada, Koji
CS Tsukuba Research Institute, Banyu Pharmaceutical Co., Ltd, Tsukuba, Ibaraki, 300-2611, Japan
SO Bioorganic & Medicinal Chemistry Letters (2003), 13(24), 4497-4499
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science B.V.
DT Journal
LA English
RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l2 10 13 abs

L2 ANSWER 10 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN

AB The neuropeptides orexin A and B (also known as hypocretins) play an important role in many physiol. and behavioral activities. Orexins are ligands of two closely related G-protein-coupled receptors, that are the named orexin 1 and orexin 2 receptors. To clearly identify the minimal ligand sequences required for receptor activation, we synthesized and analyzed different centrally, C- and N-terminally truncated analogs of orexins A and B. Furthermore, we used the shortest active analog to screen for important amino acid residues by L-alanine and L-proline replacement scans. For orexin A, only full-length peptides were able to show the same activity as orexin A, but interestingly, reduced orexin A and natural orexin A, which contains the two disulfide bonds, had the same activity. The shortest highly active orexin B analog was orexin peptide. In addition, we identified orexin A peptide as the first analog with orexin 1 receptor preference and orexin B peptide, [A27]orexin B peptide, and [P11]orexin B peptide as being highly potent **orexin 2 receptor** selective (>1000-fold) peptides.

L2 ANSWER 13 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
AB Objective. To evaluate the effects of high-fructose diet on expression of orexin and its receptors, orexin 1 receptor (OX1R) and **orexin 2 receptor** (OX2R) in rat hypothalamus tissue, and to anal. the interaction of related factors involved in regulating orexin and its receptors. Methods. Insulin resistance rat model induced by high fructose confirmed by the gold standard euglycemic clamping was employed and mRNA expression of orexin and its receptors OX1R and OX2R in hypothalamus, mRNA expression of leptin in adipose tissue were measured by reverse transcription polymerase chain reaction. Serum insulin and triglyceride levels were measured by chemiluminescence immunoassay and biochem. enzyme techniques. Results. Expression of orexin mRNA decreased about 40% in high fructose diet rats compared to control group ($P<0.01$) , whereas expression of orexin 1 receptor and **orexin 2 receptor** mRNA increased up to 4.4 and 5.1 fold ($P<0.01$). Leptin mRNA expression in adipose tissue increased about 30% in comparison with control group ($P<0.01$). Blood glucose, serum insulin and triglyceride have shown significant higher levels than those in control group ($P<0.01$). Glucose infusion rate (GIR60-120) was much lower in comparison with control group ($P<0.01$). Conclusions. High- fructose diet induces insulin resistance in rats with impact on orexin anal leptin regulations. Blood glucose, serum insulin, lipid metabolism and leptin play an interactive role on orexin and its receptors regulation in rats.

=> d l2 12

L2 ANSWER 12 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:928900 CAPLUS
DN 140:174444
TI N-Acyl 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline: The first **orexin-2 receptor** selective non-peptidic antagonist
AU Hirose, Masaaki; Egashira, Shin-Ichiro; Goto, Yasuhiro; Hashihayata, Takashi; Ohtake, Norikazu; Iwaasa, Hisashi; Hata, Mikiko; Fukami, Takehiro; Kanatani, Akio; Yamada, Koji
CS Tsukuba Research Institute, Banyu Pharmaceutical Co., Ltd, Tsukuba, Ibaraki, 300-2611, Japan
SO Bioorganic & Medicinal Chemistry Letters (2003), 13(24), 4497-4499
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science B.V.
DT Journal
LA English
RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l2 12 abs

L2 ANSWER 12 OF 37 CAPLUS COPYRIGHT 2004 ACS on STN

AB The identification of potent and selective **orexin-2 receptor** (OX2R) antagonists is described based on the modification of N-acyl 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline analog , recently discovered during high throughput screening (HTS). Substitution of an acyl group in N-acyl 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline analog with tert-Leucine (tert-Leu), and introduction of a 4-pyridylmethyl substituent onto the amino function of tert-Leu improved compound potency, selectivity, and water solubility Thus, tetrahydroisoquinoline compound is a promising tool to investigate the role of orexin-2 receptors.

=>